Research Square

Preprints are preliminary reports that have not undergone peer review. They should not be considered conclusive, used to inform clinical practice, or referenced by the media as validated information.

Risk Factors for Transfusion-Related Acute Lung Injury in Critical Patients Admitted in Intensive Care Unit: A Systematic Review and Meta-Analysis

Lunyang Hu
Changhai Hospital
Baoli Wang
Changhai Hospital
Yong Jiang
Changhai Hospital
Banghui Zhu
Changhai Hospital
Chen Wang
Changhai Hospital
Qing Yu
Changhai Hospital
Wenjia Hou
Changhai Hospital
Zhaofan Xia
Changhai Hospital
Guosheng Wu (18019359841@163.com)
Changhai Hospital
Yu Sun
Changhai Hospital

Research

Keywords: TRALI, ICU, Risk factors, Predictors

DOI: https://doi.org/10.21203/rs.3.rs-52231/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License

Abstract

Background: Until now, transfusion-related acute lung injury (TRALI) has been considered to be the leading cause of blood transfusion-related diseases and death. And there is no clinically effective treatment plan for TRALI. The aim of this study was to systematically summarize the literature on risk factors for TRALI in critical patients.

Methods: Electronic searches (up to March 2020) were performed in the Cochrane Library, Web of Knowledge, Embase, and PubMed databases. We included studies reporting on the risk factors of TRALI for critical patients and extracted the risk factors. Finally, third studies met the inclusion criteria.

Results: We summarized and analyzed the potential risk factors of TRALI for critical patients in 13 existing studies. The host-related factors were age (odds ratio (OR) [95% confidence interval] = 1.16 [1.08-1.24]), sex (OR = 1.26 [1.16-1.38]), tobacco use status (OR = 3.82 [1.91-7.65]), chronic alcohol abuse (OR = 3.82 [2.97-26.83]), fluid balance (OR = 1.24 [1.08-1.42]), shock before transfusion (OR = 4.41 [2.38-8.20]), and ASA score of the recipients (OR = 2.72 [1.43-5.16]). The transfusion-related factors were the number of transfusions (OR = 1.40 [1.14-1.72]) and fresh frozen plasma (FFP) units (OR = 1.21 [1.01-1.46]). The device-related factor was mechanical ventilation (OR = 4.13 [2.20-7.76]).

Conclusions: The risk factors for TRALI in this study included age, sex, tobacco use, chronic alcohol abuse, fluid balance, shock before transfusion, ASA score, number of transfusions, FFP units and mechanical ventilation. Our study suggests that host-related risk factors play a more important role in the occurrence and development of TRALI than blood transfusion-related risk factors.

Introduction

Many severely injured patients often suffer from hemorrhagic shock, requiring transfusion therapy. However, blood transfusion is a "double-edged sword." Transfusion-related acute lung injury (TRALI) that occasionally occurs during blood transfusion can be life-threatening[1, 2]. TRALI has been the leading cause of transfusion-related deaths since 2003 according to the US Food and Drug Administration (FDA)[3].

According to the standardized definition of TRALI, based on the consensus conference of the Canadian Blood Services (CBS) in 2004, TRALI was defined as respiratory distress and acute lung injury (ALI) that develops during blood transfusion or within 6 hours after blood transfusion, manifested as acute hypoxemia and non-cardiogenic pulmonary edema, in the absence of other risk factors for ALI[4-6]. TRALI has traditionally been considered to be a combination of two events. The “first event” is the inflammatory state of the recipient, which leads to the activation of neutrophils in the lungs. The "second event" is further activation of neutrophils caused by biologically active lipids or sensitizing antibodies contained in blood products, with subsequent pulmonary leakage[7-9]. TRALI is particularly evident in critically ill patients because most of them have different degrees of inflammation, so it is very easy to trigger the activation of neutrophils. The two-event model of TRALI may explain the high incidence rate of TRALI in this population[10, 11].

Until now, TRALI was considered to be the leading cause of blood transfusion-related diseases and death[12-14]. Generally, the incidence of TRALI varies between 0.08% and 15%[15]. The mortality rate of TRALI ranges between 5% and 14%[16-18]. This wide difference may be due to the lack of a unified standard definition of TRALI and the difference in research design. TRALI is often underestimated and underreported[19, 20]. Similar to ALI/acute respiratory distress syndrome (ARDS), supportive care measures and restrictive blood transfusion policies are mainly adopted in cases of TRALI, as there is no clinically effective treatment plan[6].

By clarifying the risk factors of a disease and their significance, it is possible to put forward practical and effective risk factor intervention strategies and prevent the occurrence and development of that disease[21]. Some previous retrospective studies have attempted to identify the risk factors associated with TRALI in critically ill patients. Prior studies have shown that routine exclusion of fresh frozen plasma (FFP) from the blood of female blood donors can reduce the incidence of TRALI[22, 23]. There was also evidence that cardiac surgery increased the risk of TRALI[7, 9]. However, most of these studies were limited because they had a retrospective study design, single-center design, and examined one or several variables. The sample size of some studies was also relatively small, and it was difficult to obtain significant results[18, 24-29]. In order to solve these problems, we performed a systematic review and meta-analysis of risk factors related to TRALI in critically ill patients.

Methods

Data Sources and retrieval Strategy

Two reviewers (L.Y.H. and B.L.W.) independently conducted systematic literature searches of the Cochrane Library, Web of Knowledge, Embase, and PubMed databases from inception up to March 2020. The following search terms were used: (Blood Transfusion* OR Transfusion Reaction*) AND (Acute Respiratory Distress Syndrome* OR acute lung injury*) AND (risk OR predict*). The references of relevant articles were also hand searched to find other relevant researches. There were no restrictions on year of publication. The detailed literature search strategy can be found in **Supplementary Table E1**.

Inclusion criteria and study selection

The studies had to meet the following inclusion criteria: (1) All patients were admitted to the ICU and received blood transfusion therapy, (2) provided clear definition and diagnosis according to the international definition of TRALI developed by the American-European Consensus Conference in 2004, (3) examined one or more indicators of the risk of TRALI, (4) examined potential risk factors for TRALI that have been previously examined by at least two studies, and (5)

published in English language. Both prospective and retrospective studies were considered eligible. Only after studying the different risk factors, overlapping studies were included in the systematic review. Reviews and case reports were also excluded.

Data extraction

The following data were independently extracted by two reviewers (L.Y.H. and B.L.W.): first author, study design and year of study, country of study, definition of TRALI, study population characteristics, types of blood transfusion products, risk factors, and indexes representing clinical outcomes. Differences between the authors were resolved by consensus at a meeting. When the research data were not fully available, the corresponding author was requested to provide more information via email.

Quality assessment

Two reviewers (L.Y.H. and B.L.W.) used the Newcastle–Ottawa Scale (NOS) to independently assess the quality of the research in this meta-analysis[30]. The scale has the following three columns: quality of selection (three items, three points), comparability (three items, three points), and assessment of outcome (three items, three points). A total score of nine points can be obtained. Studies with scores of 1–3 were classified as low-quality literature, 4–6, as medium-quality literature, and 7–9, as high-quality literature[31]. Differences arising in the scoring process were resolved through a discussion until a consensus was reached.

Statistical analysis

After extracting the data, the basic information of blood transfusion patients and the important risk factors of TRALI identified in the individual studies were integrated. Review Manager 5.1 and Stata 11.0 software were used for the meta-analysis and analysis of the risk factors related to TRALI, respectively. Continuous variables were analyzed by calculating the weighted average difference and 95% confidence intervals (CIs). Odds ratio (OR) and 95% CI were used to analyze the categorical variables. Quantitative meta-analysis of factors detected in at least two studies was performed. Cochrane's I2 index and Q test P value were used to assess the heterogeneity across included studies. Fixed effects and random effects models were used to analyze and calculate the overall effects. If the I2 value exceeded 50%, it indicated significant heterogeneity and the random-effects model was applied, which used the DerSimonian and Laird estimate. When no statistical heterogeneity was detected, a fixed-effect model was used. Egger’s regression asymmetry test and Begg funnel plot method were used to evaluate publication bias. If the funnel plot was visually symmetrical or P >0.05, it indicated no publication bias. All statistical tests were two-sided with P values of <0.05, indicating statistical significance.

Results

Study selection

We retrieved 800 potentially relevant documents from PubMed (n = 81), Embase (n = 244), Web of Science (n = 324), Cochrane Library (n = 88), or manual search (n = 3). After combining and deleting duplicate documents, 609 studies were retained. According to the title and abstract, preliminary screening was conducted to further exclude 549 articles. Subsequently, we obtained the full text of the remaining 60 articles and screened them by reading. Four of these studies were excluded because they did not provide access to the full text; 9 studies were not relevant to our theme. The inclusion and exclusion criteria of the research groups of 22 studies did not meet the conditions we defined, 5 studies did not establish a control group, 5 studies did not report on TRALI-related risk factors, and 2 studies were conference summaries. Finally, we included 13 articles in the meta-analysis. The details of the screening are shown in **Figure 1**.

Study characteristics and quality evaluation

The 13 articles included in this study included a total of 11,380,242 participants: 3179 cases and 11377063 controls. These studies were published from 2004 to 2015. The research participants originated from four countries: the United States, the Netherlands, Croatia, and Italy. The sample size varied from 26 to 11,378,264. The 13 studies were all case-control studies. Three articles were multi-center studies. We used the NOS to assess the quality of each study. Three studies scored seven points, eight studies scored eight points, and two studies scored nine points. Quality assessments indicated that all included studies had high quality. **Table 1** and **Supplementary Table E2** show the basic characteristics of all included studies and the NOS-based scoring results.

Table 1
Characteristics of all the included studies

Author	Country	Year	Intervention	Study period	Study type	Number of patients (TRALI / transfused controls)	Male	Age
Toy et al	America	2015	TRALI patients versus transfused controls	2006-2009	case-control study	308(145/163)	75(52)/90(55)	58±19/56±20
Mulder et al	the Netherlands	2014		2009-2012		304(21/283)	13(61.9)/172(60.8)	4.6±5.2/5±5.8
Menis et al	America	2014		2007-2011		11378264(2556/11375708)	1125(44)/4891555(43)	-
Zah-Bogović et al	Croatia	2014		2009-2010		252(32/220)	24(75)/138(62.7)	62.6±10.85/66.3±10.28
Teofili et al	Italy	2014		2005-2011		71(14/57)		34.4±5.8/34.4±4.8
Toy et al	America	2012		2006-2009		253(89/164)	44(49)/91(56)	54±20/56±20.2
Vlaar et al	the Netherlands	2011		2006-2009		48(16/32)	12(75)/20(63)	74±7.4/67±9.3
Vlaar et al	the Netherlands	2010		2004-2007		218(109/109)	70(64)/66(61)	59±17/57±16
Edens et al	America	2010		2008-2009		66(22/44)	-	28.3±7.5/28.2±8.6
Sanchez et al	America	2007		2002-2004		26(6/20)	3(50)/14(70)	-
Gajic et al	America	2007		2 years		148(74/74)	37(50)/37(50)	64(52-78)/61(53-73)

Silverboard et al	America	2005	2000-2002	102(35/67)	22(63)/56(84)	38.7±14.4/31.2±16.7
Gajic et al	America	2004	2001-2002	182(60/121)	33(55)/71(59)	65(50-75)/68(53-77)

TRALI, transfusion-related acute lung injury; RBC, red blood cell; FFP, fresh frozen plasma; PLT, blood platelet; NOS, Newcastle-Ottawa Scale.

Risk factors

The current meta-analysis summarizes 20 potential risk factors from four aspects, which have been reported in at least two studies: host-related, blood transfusion-related, device-related, and surgery-related factors (**Supplementary Table E3**). **Figure 2** shows the forest plots of potential risk factors predisposing patients to TRALI.

Host-related factors

Age. Two studies, including 11378312 patients, showed that the age of blood transfusion patients was significantly related to the occurrence of TRALI. The greater the age, the greater the risk. There was no obvious heterogeneity in the studies (fixed effect model, i2 = 15.9%; OR = 1.16, 95% CI = 1.08–1.24, P < 0.01; **Figure 2A**).

Sex. Two studies including 11378290 patients indicated a significant correlation between sex and the occurrence of TRALI. TRALI is more likely to occur in women than in men undergoing blood transfusion treatment. There was no obvious heterogeneity in the studies (fixed effect model, i2 = 0.0%; OR = 1.26, 95% CI = 1.16–1.38, P < 0.01; **Figure 2B**).

Tobacco use. Three studies including 11378825 patients indicated a significant correlation between tobacco use and the occurrence of TRALI. There was no obvious heterogeneity in the studies (fixed effect model, I2 = 0.0%; OR = 3.82, 95% CI = 1.91–7.65, P < 0.01; **Figure 2C**).

Chronic alcohol abuse. Two studies including 561 patients indicated a significant correlation between chronic alcohol abuse and the occurrence of TRALI. There was no obvious heterogeneity in the studies (fixed effect model, I2 = 0.0%; OR = 3.82, 95% CI = 2.97–26.83, P < 0.01; **Figure 2D**).

Tidal volume. When the two studies that reported tidal volume were aggregated, tidal volume was not associated with the occurrence of TRALI. There was some heterogeneity in the studies (random effect model, I2 = 52.2%; OR = 1.37, 95% CI = 0.89–2.11, P = 0.155 > 0.05; **Figure 2E**).

Fluid balance. Two studies including 561 patients indicated a significant correlation between fluid balance and the occurrence of TRALI. There was a high degree of heterogeneity in the studies (random effect model, I2 = 71.3%; OR = 1.24, 95% CI = 1.08–1.42, P < 0.01; **Figure 2F**).

Liver disease. Two studies including 505 patients indicated that liver disease had no significant effect on the occurrence and development of TRALI. There was a high degree of heterogeneity in the studies (random effect model, I2 = 85.5%; OR = 1.51, 95% CI = 0.48–4.78, P = 0.482 > 0.05; **Figure 2G**).

Sepsis. Three studies including 11378786 patients indicated that sepsis had no significant effect on the occurrence and development of TRALI. There was a high degree of heterogeneity in the studies (random effect model, I2 = 93.9%; OR = 2.08, 95% CI = 0.46–9.28, P = 0.339 > 0.05; **Figure 2H**).

Hematology-oncology. Three studies including 11378543 patients indicated that hematology-oncology had no significant effect on the occurrence and development of TRALI. There was a high degree of heterogeneity in the studies (random effect model, I2 = 87.9%; OR = 1.40, 95% CI = 0.25–7.80, P = 0.701 > 0.05; **Figure 2I**).

Shock before transfusion. Two studies including 561 patients indicated that patients with shock before blood transfusion were more likely to experience TRALI after blood transfusion. There was no obvious heterogeneity in the studies (fixed effect model, I2 = 0.0%; OR = 4.41, 95% CI = 2.38–8.20, P < 0.01; **Figure 2J**).

ASA score. Two studies including 300 patients indicated that transfusion patients with a high ASA score were likely to develop TRALI. There was no obvious heterogeneity in the studies (fixed effect model, I2 = 0.0%; OR = 2.72, 95% CI = 1.43–5.16, P < 0.01; **Figure 2K**).

Transfusion-related factors

Amount of transfusions. Seven studies including 976 patients indicated a significant correlation between large-scale blood transfusion and the occurrence of TRALI. There was a high degree of heterogeneity in the studies (random effect model, I2 = 77.4%; OR = 1.40, 95% CI = 1.14–1.72, P < 0.01; **Figure 2L**).

Blood products from female donors. Four studies including 553 patients indicated that blood products from female donors had no significant effect on the occurrence and development of TRALI. There was no obvious heterogeneity in the studies (fixed effect model, I2 = 20.0%; OR = 1.09, 95% CI = 0.94–1.27, P = 0.319 > 0.05; **Figure 2M**).

RBC units. Five studies including 519 patients indicated that the number of RBC units had no significant effect on the occurrence and development of TRALI. There was some heterogeneity in the studies (random effect model, I2 = 58.8%; OR = 0.97, 95% CI = 0.72–1.31, P = 0.859 > 0.05; **Figure 2N**).

PLT units. Five studies including 11378475 patients indicated that the number of PLT units had no significant effect on the occurrence and development of TRALI. There was some heterogeneity in the studies (random effect model, I2 = 69.6%; OR = 1.38, 95% CI = 0.27–1.26, P = 0.160 > 0.05; **Figure 2O**).

FFP units. Five studies including 393 patients indicated a significant correlation between the number of FFP units and the occurrence of TRALI. There was some heterogeneity in the studies (random effect model, I2 = 71.1%; OR = 1.21, 95% CI = 1.01–1.46, P = 0.043 < 0.05; **Figure 2P**).

Device-related factors

Mechanical ventilation. Three studies including 775 patients indicated that patients on mechanical ventilation during blood transfusion therapy were more likely to develop TRALI. There was no obvious heterogeneity in the studies (fixed effect model, I2 = 0.0%; OR = 4.13, 95% CI = 2.20–7.76, P < 0.01; **Figure 2Q**).

Pump time during cardiopulmonary bypass. Two studies including 300 patients indicated that pump time during cardiopulmonary bypass had no significant effect on the occurrence and development of TRALI. There was a high degree of heterogeneity in the studies (random effect model, I2 = 95.6%; OR = 1.04, 95% CI = 0.96–1.12, P = 0.329 > 0.05; **Figure 2R**).

Procedure-related factors

Surgical intervention. Two studies including 97 patients indicated that surgical intervention had no significant effect on the occurrence and development of TRALI. There was no obvious heterogeneity in the studies (fixed effect model, I2 = 0.0%; OR = 1.21, 95% CI = 0.17–8.63, P = 0.848 > 0.05; **Figure 2S**).

Liver transplantation. Three studies including 587 patients indicated no significant correlation between liver transplantation and the occurrence of TRALI. There was no obvious heterogeneity in the studies (fixed effect model, I2 = 15.1%; OR = 2.95, 95% CI = 0.80–10.84, P = 0.188 > 0.05; **Figure 2T**).

Publication Bias and sensitivity analysis

We used the Begg funnel plot and Egger linear regression test to evaluate the publication bias in these studies. Because each factor was generally included in a few studies, we only conducted a bias test for risk factors that were included in more than three studies. The assessment of publication bias for potential risk factors of TRALI is shown in **Supplementary Table E4.** Among the factors that had a significant correlation with the occurrence of TRALI, the number of transfusions had some publication bias, and the number of FFP units did not. Among the factors that were not significantly related to TRALI, there was no publication bias for blood products from female donors and number of RBC units and PLT units (**Figure 3**). Because the number of studies included was small, we did not conduct a sensitivity analysis.

Discussion

To the best of our knowledge, this is the first meta-analysis of risk factors of TRALI in critically ill patients. We summarized and analyzed the potential risk factors of TRALI for critical patients in 13 existing studies. The risk factors were related to the age, sex, tobacco use status, chronic alcohol abuse, fluid balance, shock before transfusion, and ASA score of the recipients. The number of transfusions and FFP units were risk factors related to blood transfusion. The risk factor related to the device was mechanical ventilation. Tidal volume, liver disease, sepsis, blood tumor disease, blood products from female blood donors, red blood cell units, platelet units, pumping time during extracorporeal circulation, surgery, and liver transplantation were not identified as risk factors of TRALI. Some of these conclusions seem to be logical, but our research findings strengthen previous evidence. However, some evidence was contrary to previous conclusions, as will be discussed below.

In 1951, Barnard reported that an acute leukemia patient died because of the acute lung reaction caused by an allergic reaction to blood transfusion, which was the first report of lung injury due to blood transfusion[32]. After that, several scientists reported similar cases. Until the 1980s, TRALI was officially recognized as an independent disease[33]. In 2004, the consensus meeting held by the CBS Agency standardized two entities for the first time: TRALI and possible TRALI (pTRALI), which means that the cause of ALI is not clear; it could be ARDS or the factor of blood transfusion[3, 34]. In 2005, the definition of the CBS was expanded to include patients with ALI deterioration due to blood transfusion and to determine whether they had TRALI or ARDS according to clinical standards and judgments[34]. In 2019, researchers used the Delphi Methodology to re-classify TRALI into two types: TRALI I (without risk factors of ARDS) and TRALI II (with risk factors of ARDS or existing mild ARDS)[35, 36]. In the 14 years after the CBS published the guideline, a large amount of information from prospective and retrospective research related to TRALI has been accumulated. A careful reading of the literature will show that previous definitions have not been strictly applied, and there is a large degree heterogeneity in the incidence rates and mortality rates. In conclusion, the problems may be as follows: (1) The clinical manifestations and laboratory tests of TRALI were not independent pathological features, so it was difficult to differentiate diagnosis, and the tools to perform these diagnostic analysis were not extensive enough[37]. (2) Except for the measurement of blood oxygen saturation (PaO2/FiO2), there was no objective laboratory test in the diagnostic criteria, so the diagnosis was rather subjective[2]. (3) Some previous studies have shown that the risk factors of ARDS and TRALI may be similar, which leads to unclear taxonomic boundaries of TRALI and ARDS, making it almost impossible to distinguish TRALI from other ALIs in clinical practice[35]. (4) According to the definition, TRALI appears temporarily within 6 hour after blood transfusion, but a few cases have been reported to occur between 6 hours and 48 hours after blood transfusion, emphasizing the need for a standardized definition of TRALI[38]. So far, although there is a relatively large number of studies on TRALI, the inclusion criteria for the TRALI population were not uniform among the studies, and the sample size in some studies is relatively small, the pathogenesis is unclear, and the research results are different.

Since the diagnostic criteria of TRALI in previous studies are not uniform, and in order to understand the risk factors of TRALI comprehensively, this study included studies on TRALI and pTRALI as per the definition of the CBS. According to the Berlin standard published in 2012, the term "acute lung injury" has been eliminated, and according to the degree of hypoxia, ARDS was divided into mild, moderate, and severe[36]. For this reason, we also included cases of transfusion-related ARDS in the case group. Finally, the current 13 studies were included.

In terms of host-related risk factors, our study found that as patients aged, the risk of TRALI increased. Some studies have shown that in the elderly population, most exhibited chronic low-grade inflammation, which is manifested by high baseline levels of pro-inflammatory cytokines in the body, likely to cause TRALI[39]. In addition, women who receive blood transfusions are more likely than men to develop TRALI. Previous studies have found that HLA I, HLA II, and granulocyte antibodies are common in women who have given birth. When these antibodies encounter homologous antigens from the transfusion plasma, it can lead to neutrophil activation and oxidative substance release, which can damage the lung endothelium[40, 41]. This shows that previous pregnancy experience is a very important factor leading to TRALI. Chronic alcohol abuse can also increase the risk, possibly since the level of glutathione, an antioxidant in the lungs, decreases, which in turn reduces the phagocytic function of the apoptotic cells, resulting in increased inflammation in the lungs[27]. Patients with a history of smoking have varying degrees of respiratory problems, which increase the risk of disease[42]. Shock can cause tissue damage and may induce TRALI by activating the patient's neutrophils[35]. The ASA score reflects the physical condition of the patient, and a high score will increase the risk of illness[43].

In terms of transfusion-related factors, our study found that the amount of transfusion and number of FFP units were significantly related to the occurrence of TRALI, while female sex of the donors and number of RBC units and PLT units did not seem to significantly increase the risk of TRALI. Since 2003, in order to reduce the incidence of TRALI, the British government mandated that female plasma be used in manufacturing. Since the implementation of this approach, the number of TRALI cases in the UK has indeed decreased[18]. The only test that can be used to diagnose TRALI is to monitor the content of HLA and granulocyte antibodies in the plasma of the recipient or donor. The principle is that the relevant antigens and antibodies contained in the donor and recipient will induce related inflammatory reactions, which will lead to lung injury. The discovery of antigen-antibody reactions strongly supports the diagnosis of TRALI. However, in one study, we did not find the consistency between antigens and antibodies in 15% of TRALI cases, suggesting that a simple antigen-antibody reaction does not necessarily lead to clinical TRALI[44]. In a retrospective study, Toy et al. investigated a group of female donors who had experience in production, and they had multiple antibodies related to HLA antigens. TRALI did not occur when the donated blood was transfused to 55 patients with non-neutropenia of known HLA type[45]. In this regard, some researchers believe that the occurrence of TRALI may require two different events: one is related to the clinical situation of the recipient (such as active infection), and the other one is related to the infusion of blood products containing HLA antibodies or granulocyte antibodies or other biological response regulators[44].

In this study, we found that most host-related risk factors are characterized by a pro-inflammatory state, which may stimulate lung neutrophils as the "first attack" in the development of TRALI[46]. Therefore, the clinical state of the host may lead to a decrease in lung compliance before blood transfusion, and a deterioration in lung compliance after blood transfusion, which may lead to lung injury[47]. More studies show that host-related risk factors play a more critical role in the development of TRALI than transfusion-related risk factors. This conclusion highlights the importance of the "first attack" mentioned above[9].

In terms of device-related risk factors, we found that mechanical ventilation is significantly related to the occurrence of TRALI. A previous study showed that mechanical ventilation accelerates and aggravates lung injury[48]. When the peak airway pressure is >30 cm H_20, the risk of ALI increases significantly[49, 50]. The above conclusions suggest that mechanical ventilation also plays an important role in triggering TRALI in the early stage and a synergistic role in the later stage with blood transfusion in the development of lung injury.

Our study has some advantages and limitations. By formulating a systematic research plan, a comprehensive search strategy, and strict inclusion and exclusion criteria and by evaluating the research quality, the objectivity and consistency of this study can be considered high. The findings could help both surgeons and patients interpret the current evidence.

Although the research is innovative, some limitations should be recognized. First of all, the majority of the studies included in the analysis were retrospective studies, and the diversity and complexity of TRALI-related influencing factors were affected to a certain extent by selection bias. Second, there were very few studies on some risk factors. In this case, the power of these factors is too weak to find a significant association with a relatively small impact. We believe that as the number of powerful cohort studies increases, clearer and higher levels of evidence will become available. Third, because some data are lacking (such as APACHE II), some potential risk factors could not be analyzed in groups. Finally, because the diagnostic criteria of TRALI have not been completely unified, there is variability in the diagnosis of TRALI in some studies. In this regard, we formulated the inclusion criteria for meta-analysis according to the needs of this study to provide guidance for clinicians as soon as possible.

Conclusion

TRALI is considered the main cause of blood transfusion-related illness and deaths in critically ill patients. Age, sex, tobacco use, chronic alcohol abuse, fluid balance, shock before transfusion, ASA score, number of transfusions, FFP units and mechanical ventilation were risk factors of TRALI. This study suggests that host-related risk factors play a more important role in the occurrence and development of TRALI than blood transfusion-related risk factors. Our findings may help clinicians formulate accurate and effective prevention and treatment strategies and provide appropriate and timely treatment. Furthermore, it is necessary to establish clear and unified diagnosis criteria for TRALI, to study the pathogenesis of TRALI, and to conduct studies with large sample sizes on the prevalence and risk factors of TRALI.

Abbreviations

TRALI: transfusion-related acute lung injury; FDA: Food and Drug Administration; CBS: Canadian Blood Services; ALI: acute lung injury; ARDS: acute respiratory distress syndrome; FFP: fresh frozen plasma; NOS: Newcastle–Ottawa Scale; CL: confidence interval; OR: odds ratio; RBC: red blood cell; PLT: platelet

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no conflicts of interest.

Funding

There was no funding source for this study.

Authors' contributions

LYH have full access to all of the data in the study. All authors of the manuscript are accountable for all aspects of the accuracy and integrity of the manuscript. Study conception and design: LYH, ZFX, GSW and YS; data acquisition: LYH and BLW; statistical analysis: LYH, BLW and GSW; interpretation of the data: all authors; drafting of the manuscript: all authors; critical revision of the manuscript for important intellectual content: all authors; Final approval of the manuscript: all authors.

Acknowledgements

Not applicable.

References

1. Kopko P, Silva M, Shulman I, Kleinman S. AABB survey of transfusion-related acute lung injury policies and practices in the United States. Transfusion. 2007. 47(9): 1679-85.
2. Zah-Bogovic T, Mesaric J, Hrabac P, Majeric-Kogler V. Possible transfusion-related acute lung injury (TRALI) in cardiac surgery patients. Croat Med J. 2014. 55(2): 138-45.
3. oy P, Gajic O, Bacchetti P, et al. Transfusion-related acute lung injury: incidence and risk factors. Blood. 2012. 119(7): 1757-67.
4. Goldman M, Webert KE, Arnold DM, et al. Proceedings of a consensus conference: towards an understanding of TRALI. Transfus Med Rev. 2005. 19(1): 2-31.
5. Kleinman S. A perspective on transfusion-related acute lung injury two years after the Canadian Consensus Conference. Transfusion. 2006. 46(9): 1465-8.
6. Mulder HD, Augustijn QJ, van Woensel JB, Bos AP, Juffermans NP, Wösten-van Asperen RM. Incidence, risk factors, and outcome of transfusion-related acute lung injury in critically ill children: a retrospective study. J Crit Care. 2015. 30(1): 55-9.
7. Silliman CC, Boshkov LK, Mehdizadehkashi Z, et al. Transfusion-related acute lung injury: epidemiology and a prospective analysis of etiologic factors. Blood. 2003. 101(2): 454-62.
8. Silliman CC. The two-event model of transfusion-related acute lung injury. Crit Care Med. 2006. 34(5 Suppl): S124-31.
9. Vlaar AP, Binnekade JM, Prins D, et al. Risk factors and outcome of transfusion-related acute lung injury in the critically ill: a nested case-control study. Crit Care Med. 2010. 38(3): 771-8.
10. Gajic O, Rana R, Winters JL, et al. Transfusion-related acute lung injury in the critically ill: prospective nested case-control study. Am J Respir Crit Care Med. 2007. 176(9): 886-91.
11. Rana R, Fernández-Pérez ER, Khan SA, et al. Transfusion-related acute lung injury and pulmonary edema in critically ill patients: a retrospective study. Transfusion. 2006. 46(9): 1478-83.

12. Holness L, Knippen MA, Simmons L, Lachenbruch PA. Fatalities caused by TRALI. Transfus Med Rev. 2004. 18(3): 184-8.
13. Menis M, Anderson SA, Forshee RA, et al. Transfusion-related acute lung injury and potential risk factors among the inpatient US elderly as recorded in Medicare claims data, during 2007 through 2011. Transfusion. 2014. 54(9): 2182-93.
14. Kleinman S, Chan P, Robillard P. Risks associated with transfusion of cellular blood components in Canada. Transfus Med Rev. 2003. 17(2): 120-62.
15. Vlaar AP, Juffermans NP. Transfusion-related acute lung injury: a clinical review. Lancet. 2013. 382(9896): 984-94.
16. Benson AB, Austin GL, Berg M, et al. Transfusion-related acute lung injury in ICU patients admitted with gastrointestinal bleeding. Intensive Care Med. 2010. 36(10): 1710-7.
17. Fung YL, Silliman CC. The role of neutrophils in the pathogenesis of transfusion-related acute lung injury. Transfus Med Rev. 2009. 23(4): 266-83.
18. Sanchez R, Bacchetti P, Toy P. Transfusion-related acute lung injury: a case-control pilot study of risk factors. Am J Clin Pathol. 2007. 128(1): 128-34.
19. Kopko PM, Marshall CS, MacKenzie MR, Holland PV, Popovsky MA. Transfusion-related acute lung injury: report of a clinical look-back investigation. JAMA. 2002. 287(15): 1968-71.
20. Wallis JP. Transfusion-related acute lung injury (TRALI)–under-diagnosed and under-reported. Br J Anaesth. 2003. 90(5): 573-6.
21. Schmickl CN, Mastrobuoni S, Filippidis FT, et al. Male-predominant plasma transfusion strategy for preventing transfusion-related acute lung injury: a systematic review. Crit Care Med. 2015. 43(1): 205-25.
22. Vlaar AP, Binnekade JM, Schultz MJ, Juffermans NP, Koopman MM. Preventing TRALI: ladies first, what follows. Crit Care Med. 2008. 36(12): 3283-4; author reply 3284.
23. Eder AF, Herron RM Jr, Strupp A, et al. Effective reduction of transfusion-related acute lung injury risk with male-predominant plasma strategy in the American Red Cross (2006-2008). Transfusion. 2010. 50(8): 1732-42.
24. Teofili L, Bianchi M, Zanfini BA, et al. Acute lung injury complicating blood transfusion in post-partum hemorrhage: incidence and risk factors. Mediterr J Hematol Infect Dis. 2014. 6(1): e2014069.
25. Vlaar AP, Hofstra JJ, Determann RM, et al. The incidence, risk factors, and outcome of transfusion-related acute lung injury in a cohort of cardiac surgery patients: a prospective nested case-control study. Blood. 2011. 117(16): 4218-25.
26. Edens JW, Chung KK, Pamplin JC, et al. Predictors of early acute lung injury at a combat support hospital: a prospective observational study. J Trauma. 2010. 69 Suppl 1: S81-6.
27. Toy P, Bacchetti P, Grimes B, et al. Recipient clinical risk factors predominate in possible transfusion-related acute lung injury. Transfusion. 2015. 55(5): 947-52.
28. Silverboard H, Aisiku I, Martin GS, Adams M, Rozycki G, Moss M. The role of acute blood transfusion in the development of acute respiratory distress syndrome in patients with severe trauma. J Trauma. 2005. 59(3): 717-23.
29. Erratum for Research Article: "Single-cell RNA-seq and computational analysis using temporal mixture modeling resolves TH1/TFH fate bifurcation in malaria" by T. Lönnberg, V. Svensson, K. R. James, D. Fernandez-Ruiz, I. Sebina, R. Montandon, M. S. F. Soon, L. G. Fogg, A. S. Nair, U. N. Liligeto, M. J. T. Stubbington, L.-H. Ly, F. Otzen Bagger, M. Zwiessele, N. D. Lawrence, F. Souza-Fonseca-Guimaraes, P. T. Bunn, C. R. Engwerda, W. R. Heath, O. Billker, O. Stegle, A. Haque, S. A. Teichmann. Sci Immunol. 2018. 3(21).
30. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010. 25(9): 603-5.
31. Tan B, Zhang F, Zhang X, et al. Risk factors for ventilator-associated pneumonia in the neonatal intensive care unit: a meta-analysis of observational studies. Eur J Pediatr. 2014. 173(4): 427-34.
32. BARNARD RD. Indiscriminate transfusion: a critique of case reports illustrating hypersensitivity reactions. N Y State J Med. 1951. 51(20): 2399-402.
33. Popovsky MA, Abel MD, Moore SB. Transfusion-related acute lung injury associated with passive transfer of antileukocyte antibodies. Am Rev Respir Dis. 1983. 128(1): 185-9.
34. Toy P, Popovsky MA, Abraham E, et al. Transfusion-related acute lung injury: definition and review. Crit Care Med. 2005. 33(4): 721-6.
35. Vlaar A, Toy P, Fung M, et al. A consensus redefinition of transfusion-related acute lung injury. Transfusion. 2019. 59(7): 2465-2476.
36. Ferguson ND, Fan E, Camporota L, et al. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. Intensive Care Med. 2012. 38(10): 1573-82.
37. Semple JW, Rebetz J, Kapur R. Transfusion-associated circulatory overload and transfusion-related acute lung injury. Blood. 2019. 133(17): 1840-1853.
38. Kumar R, Sedky MJ, Varghese SJ, Sharawy OE. Transfusion Related Acute Lung Injury (TRALI): A Single Institution Experience of 15 Years. Indian J Hematol Blood Transfus. 2016. 32(3): 320-7.
39. Boe DM, Boule LA, Kovacs EJ. Innate immune responses in the ageing lung. Clin Exp Immunol. 2017. 187(1): 16-25.
40. Popovsky MA, Moore SB. Diagnostic and pathogenetic considerations in transfusion-related acute lung injury. Transfusion. 1985. 25(6): 573-7.
41. Kopko PM, Popovsky MA, MacKenzie MR, Paglieroni TG, Muto KN, Holland PV. HLA class II antibodies in transfusion-related acute lung injury. Transfusion. 2001. 41(10): 1244-8.
42. Higgins S, Fowler R, Callum J, Cartotto R. Transfusion-related acute lung injury in patients with burns. J Burn Care Res. 2007. 28(1): 56-64.
43. Choi KJ, Pham CH, Collier ZJ, et al. The Predictive Capacity of American Society of Anesthesiologists Physical Status (ASA PS) Score in Burn Patients. J Burn Care Res. 2020 .
44. Khan SY, Kelher MR, Heal JM, et al. Soluble CD40 ligand accumulates in stored blood components, primes neutrophils through CD40, and is a potential cofactor in the development of transfusion-related acute lung injury. Blood. 2006. 108(7): 2455-62.

45. Toy P, Hollis-Perry KM, Jun J, Nakagawa M. Recipients of blood from a donor with multiple HLA antibodies: a lookback study of transfusion-related acute lung injury. Transfusion. 2004. 44(12): 1683-8.
46. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985. 13(10): 818-29.
47. Wolthuis EK, Choi G, Dessing MC, et al. Mechanical ventilation with lower tidal volumes and positive end-expiratory pressure prevents pulmonary inflammation in patients without preexisting lung injury. Anesthesiology. 2008. 108(1): 46-54.
48. Slutsky AS, Ranieri VM. Ventilator-induced lung injury. N Engl J Med. 2014. 370(10): 980.
49. Iribarren C, Jacobs DR Jr, Sidney S, Gross MD, Eisner MD. Cigarette smoking, alcohol consumption, and risk of ARDS: a 15-year cohort study in a managed care setting. Chest. 2000. 117(1): 163-8.
50. Gajic O, Rana R, Mendez JL, et al. Acute lung injury after blood transfusion in mechanically ventilated patients. Transfusion. 2004. 44(10): 1468-74.

Figures

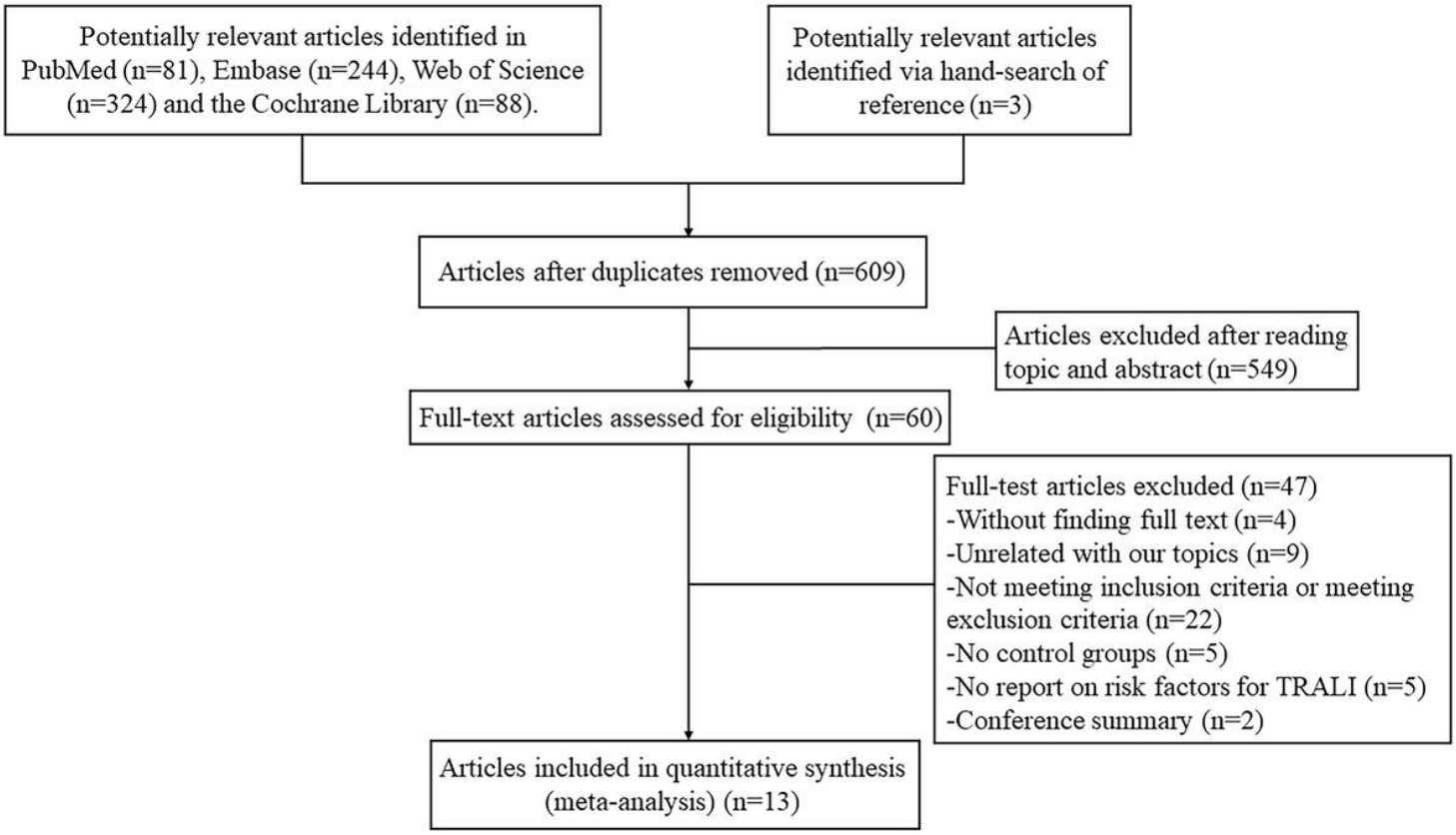

Figure 1

Flow chart of search results according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines. TRALI, transfusion-related acute lung injury.

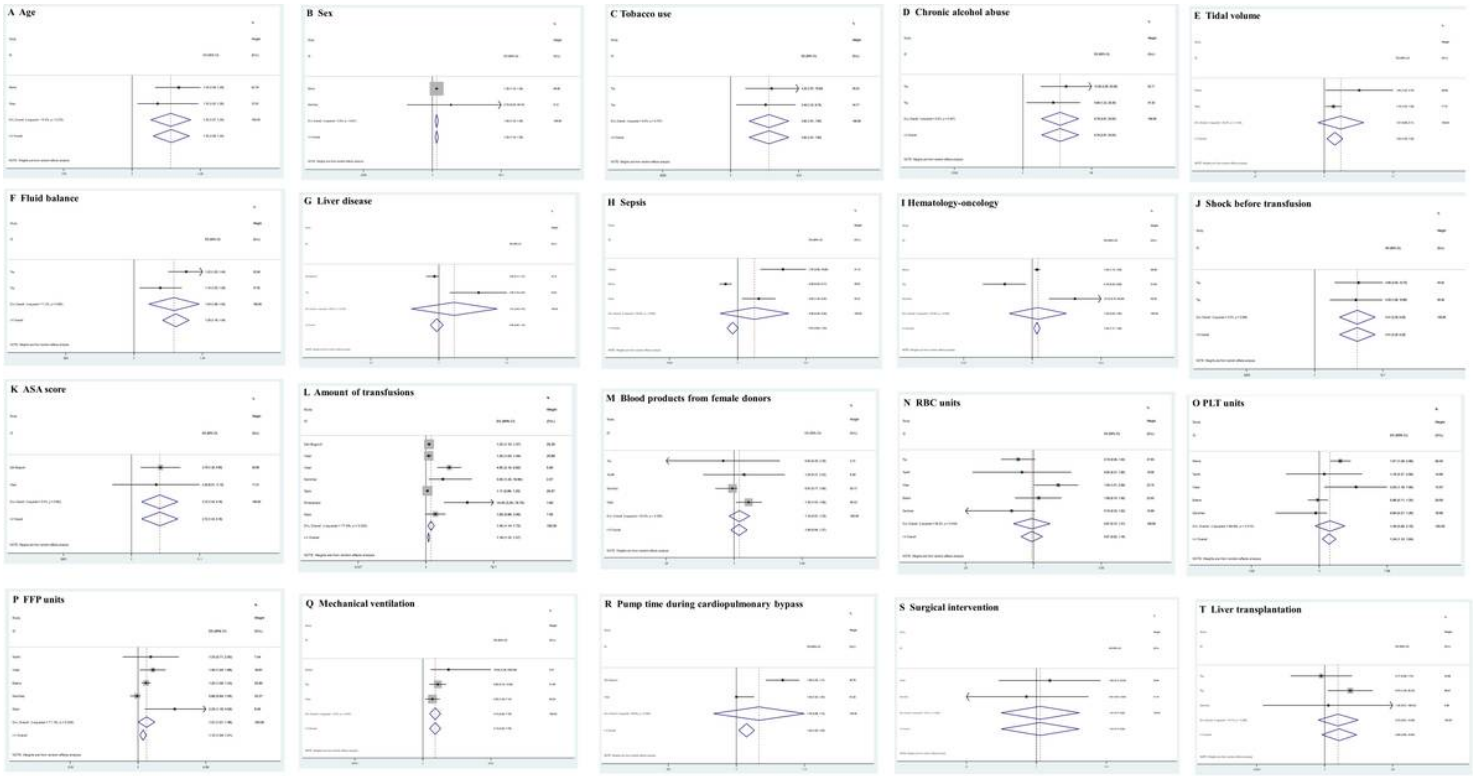

Figure 2

Forest plots of significant risk factors for TRALI with data available in at least two studies.

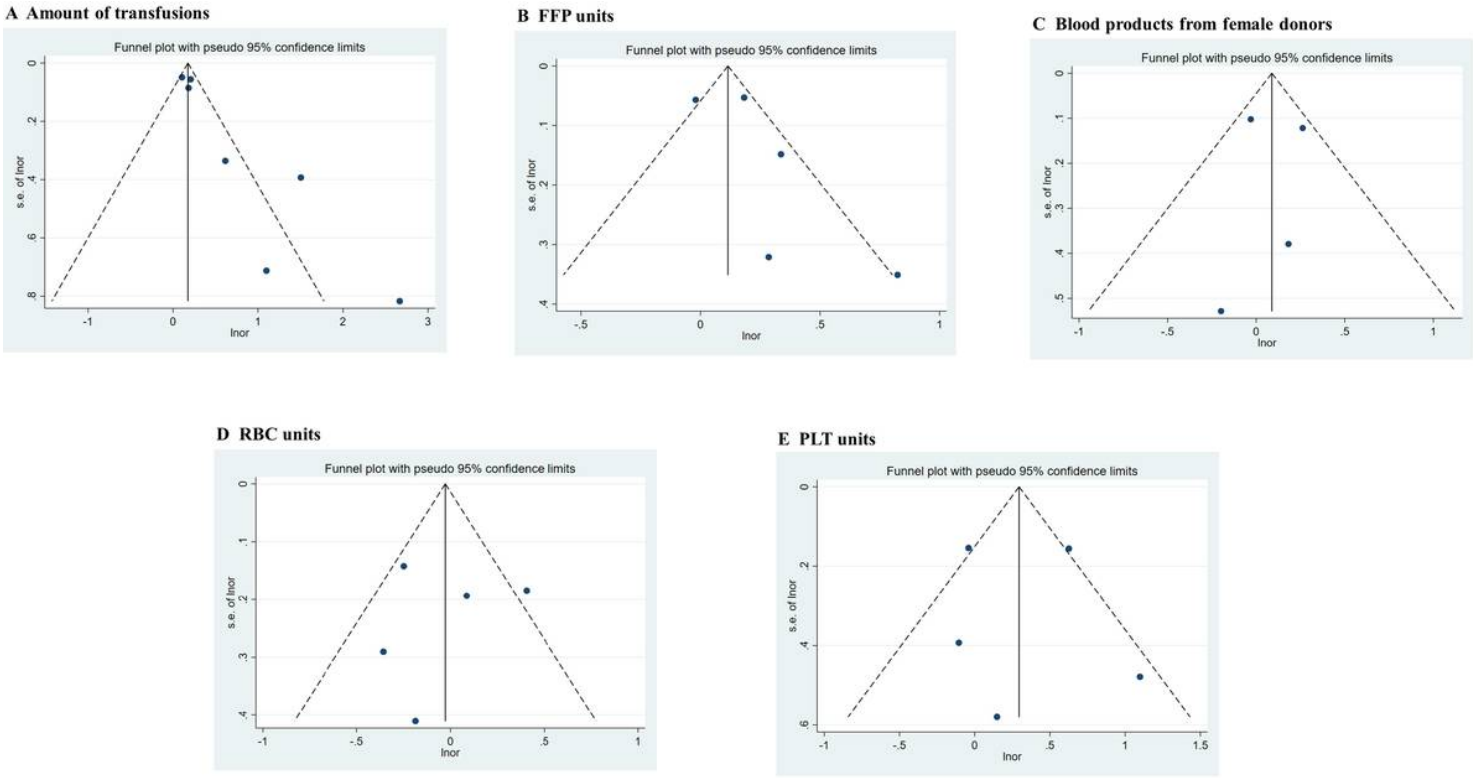

Figure 3

Bias tests of risk factors for TRALI that were included in more than three studies were conducted.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTables.docx